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Formation of Trioxadamantane type Aglucones of 3-Methoxy Secologanin Derivatives

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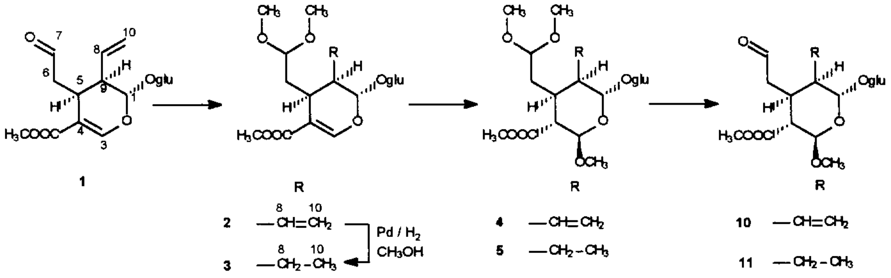
Abstract: Acidic transformation of some 3,4-dihydro-3-substituted secologanin derivatives produced trioxadamantane type compounds. The formation of the bridged tricyclic products from monocyclic educts is interpreted as multistep hydrolysis and transacetalation accompanied by deglucosylation. © 1997 Elsevier Science Ltd.

The monoterpene glucoside secologanin (**1**)[1-5] is a key intermediate in the biosynthesis of the majority of the indole and related monoterpenoid alkaloids[6,7]. As a polyfunctional compound, it undergoes a large number of regio- and stereoselective reactions. We examined the reaction of 3,4-dihydro-3-bromo and 3,4-dihydro-3-methoxy secologanin derivatives with acid.

RESULTS AND DISCUSSION

Hydro-methoxy-addition and Deglucosylation: Hydro-methoxy-addition to the heteroconjugated double bond was carried out by treatment of secologanin dimethyl acetal (**2**)[8,9] and its 8,10-dihydro derivative **3** with aqueous methanolic sodium hydroxide. After neutralisation of the reaction mixture with acidic ion exchange resin, realkylation of the partially hydrolysed carboxylic group with diazomethane gave (3*R*,4*R*)-3,4-dihydro-3-methoxysecologanin dimethyl acetal (**4**), and its 8,10-dihydro analogue **5**, respectively (Scheme 1). The tetraacetyl derivative of **4** was prepared by F. Murai and his co-workers[10], but the stereochemistry at C-3 and C-4 was not defined.

Scheme 1.



In accordance with the expected addition reaction the ^{1}H NMR spectra of compounds **4** and **5** contained signals of four methoxy groups; the signal of H-3 is shifted from the heteroconjugated olefinic region

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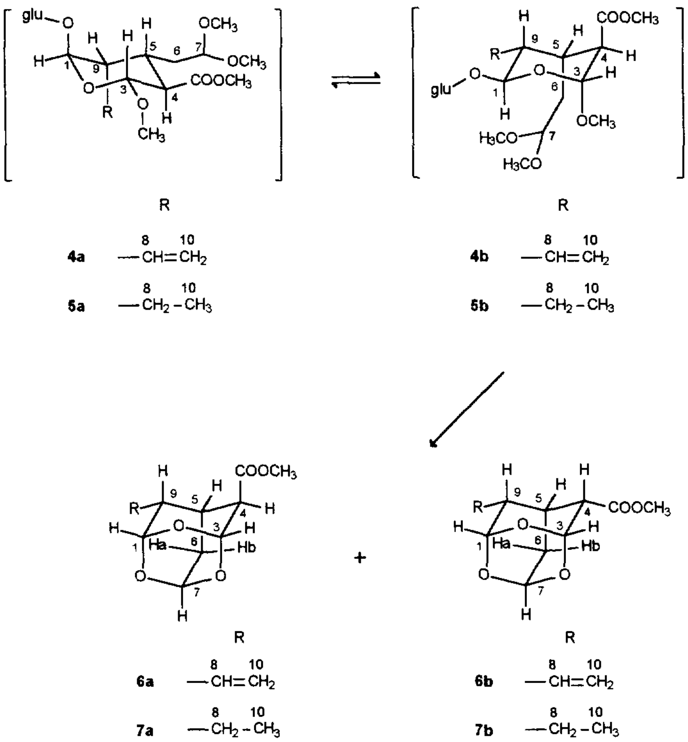
(~ 7.5 ppm) to an acetalic position (~ 5.1 ppm), and a new doublet-doublet signal appeared at about 2.3 ppm in them. The low value (1.3 Hz) of $J_{1,9}$ suggested, that the equilibrium of conformers **4a** and **4b,** as well as **5a** and **5b** is strongly shifted towards **4a** and **5a**, respectively (Scheme 2.). The high values of $J_{3,4}$ and $J_{4,5}$ (8.9 and 12.1 Hz, 8.7 and 11.7 Hz, respectively) indicated the trans diaxial positions of H-3 and H-4, as well as H-4 and H-5 atoms. The *S* configuration of C-5 could not change during the reaction, the configuration of both new chiral centers (C-3 and C-4) is *R*, in compounds **4** and **5**.

Scheme 2.



For acid-catalysed deglucosylation of compound **4**, several reaction conditions were tested and the water-toluene two phase system containing catalytic amount of aqueous hydrochloric acid was proved to be the best. The reaction product was the mixture of **6a** and **6b** C-4 epimer pair in a ratio of 7:3.

The ^{1}H NMR spectrum of the product was recorded in several solvents. The best signal dispersion was observed in benzene, so the detailed investigations were performed in this solvent. Unambiguous assignment of the ^{1}H and ^{13}C NMR spectra was gained from a homo (COSY) and a heteronuclear (Hetcorr) chemical shift correlation 2D NMR spectrum. There are two sets of signal in the ^{1}H NMR spectrum of the reaction product with the intensity ratio of 7:3. There are no signals due to a formyl group or a heteroconjugated double bond in either of the two sets, which suggests that these functional moieties have not been regenerated. In accordance with deglucosylation, the signals due to carbons and protons of the D-glucopyranosyl unit are absent in the spectra. In both signal sets one peak due to a methoxy group, and three peaks due to acetalic CH groups were identified. These facts indicated the presence of cyclic acetal units forming trioxaadamantane structures.

Table 1. Intensity enhancements of DNOE experiments

Irradiated signal	Observed nOe intensity enhancement [%]
	***6a**
H-4	H-3 3.3; H_a-6 -0.4; H_b-6 3.6
H_a-6	H-5 3.4; H_b-6 21.0; H-7 3.0; H-8 3.0
H_b-6	H-4 5.5; H-5 2.4; H_a-6 18.9; H-7 3.1
H-9	H-1 3.5; H-5 2.6; H-8 1.5; H_2-10 1.3
	***6b**
H_a-6	H-5 2.5; H_b-6 21.0; H-7 3.3; H-8 4.1
H_b-6	H-5 2.3; H_a-6 20.7; H-7 3.3
H-9	H-1 3.2; H-4 5.0; H-5 1.4; H-8 ≈1
	****8**
H-1	H_b-6 2.9; H_a-8 2.8; H-9 1.8; CH_3 O-3 0.6; H-1′ 3.7
H-3	H-5 5.1; CH_3 O-3 3.0
H-5	H-3 6.9; H_a-6 2.9; H-7 5.8; H-9 9.0
CH_3O-3	H-1 1.1; H-3 9.4; H-1′ 2.2
	*****9b**
H-1	H-3 0.7; H-5 -0.3; H_a-8 2.0; H-9 5.9; H_3-10 0.5
H-3	H-1 0.3; H-7 0.2; H-9 0.3
H_a-6	H-5 4.1; H_b-6 24.0; H-7 5.3; H_a-8 3.6; H_b-8 5.2
H_b-6	H-3 0.5; H-5 4.3; H_b-6 24.3; H-7 6.0; H_a-8 -1.9; H_b-8 -1.1
H-9	H-1 7.6; H-3 0.7; H-5 5.4; H_a-8 1.8; H_b-8 1.2; H_3-10 0.9

*: in benzene-d_6, **: in pyridine-d_5, at 60 °C, ***: in $CDCl_3$

There are 6 chiral centers in such a structure (C-1,3,4,5,7 and 9). As mentioned above, it is unlikely, that the *S* chirality of C-5 changed during deglucosylation and cyclisation. The stereochemistry of three other centres (C-1, C-3 and C-7) is fixed by the bridged trioxaadamantane ring system. Therefore the two sets of signals have to be assigned to two of the remaining four possible diastereomers. This problem was solved by difference nOe measurements, the obtained signal intensity enhancements are summarized in Table 1. Significant nOe interactions in both signal sets between H-8 and H_a-6 proved the steric proximity of the appropriate protons and the *R* configuration of C-9 in both epimers. NOe interaction was observed between H-4 and H_b-6 in the major product **6a**, and between H-9 and H-4 in the minor one **6b**, proving *R* configuration of C-4 in the former and *S* one in the latter. Moreover, ^{13}C NMR chemical shifts indicated γ-gauche interactions of the methoxycarbonyl group with C-9 in compound **6a**, and with C-6 in compound **6b**, further supporting the structures assigned above. These data proved that the sample contains two C-4 epimers which have the structures shown in Scheme 2. The energy state of the four possible stereoisomers was calculated by ALCHEMY II molecular mechanics computer program. The estimated relative energy values are given in Table 2. According to these calculations, the two isolated stereoisomers have the lowest energy states.

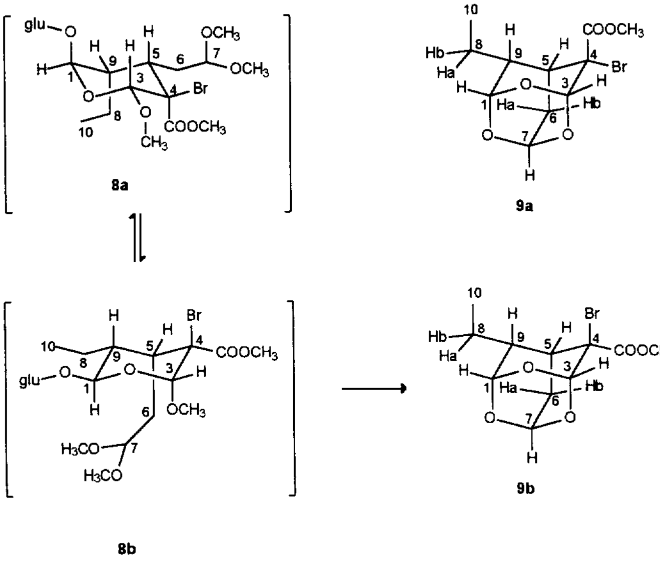
In an analogous reaction, a mixture of **7a** and **7b** C-4 epimers were prepared from compound **5.** In their ^1H NMR spectra, two sets of signals were again observed in a ratio of 17:3 (the major compound was **7a**). The close values of their chemical shifts with those of **6a** and **6b** (except, of course, the signals of the ethyl group instead of the vinyl) proved likewise their C-4 epimeric relation.

Table 2. Relative energy values of the trioxadamantane stereoisomers

	Configuration		Calculated relative energy values
	of C-4	of C-9	kcal/mol
R = vinyl group	*R*	*R*	2.0 (**6a**)
	S	*R*	2.1 (**6b**)
	S	*S*	3.4
	R	*S*	3.7
R = ethyl group	*R*	*R*	2.8 (**7a**)
	S	*R*	3.0 (**7b**)
	R	*S*	3.7
	S	*S*	4.2

Bromo-methoxy-addition and Deglucosylation: Bromo-methoxy-addition to the heteroconjugated double bond of 8,10-dihydrosecologanin dimethyl acetal **3** with dibromine in methanol in the presence of barium carbonate afforded (3*R*,4*R*)-4-bromo-3,4,8,10-tetrahydro-3-methoxysecologanin dimethyl acetal (**8**), after purification by column chromatography.

Scheme 3.



The bromo-methoxy addition to the C-3–C-4 double bond was proved by the NMR spectra. As in compound **5**, the signal of H-3 in **8** shifted from the olefinic (~7.5 ppm) to the acetalic (5.7) regio, but contrary to **5**, it appeared as a singlet. Moreover, in the ^{13}C NMR spectrum the signal of C-4 appeared as a quaternary carbon at 66.6 ppm while C-3 produced a methin signal at 100.2 ppm. These facts proved that in the addition the bromine atom is attached to C-4 and the methoxy group to C-3.

The stereochemistry of the addition was partly solved by ^{1}H NMR nOe measurements (Table 1). Considerable nOe interactions could be observed between H-3 and H-5, as well as H-1 and the protons of the 3-methoxy group, which proved their steric proximity. As it is again unlikely that the configuration of C-5 changed during the reaction, these data proved the *R* configuration of C-3. In acetone-d$_6$ at room temperature, the linewidth of some proton signals of **8** (e. g. H$_a$-6′, H$_b$-6′, H-7) is larger than usually and the value of $J_{1,9}$ (~ 6.1 Hz) is between the expected coupling constant for a diaxial (~ 10 Hz) and a diequatorial (~3 Hz) position. These facts indicate that in the six membered ring having bulky substituents the conformational interconversion is somewhat hindered causing the line broadening of the signals, and on the other hand the coupling constant data suggests that compound **8** exists in approximately 1:1 equilibrium of the two conformers **8a** and **8b**. Configuration of C-4 could not be determined from the spectra.

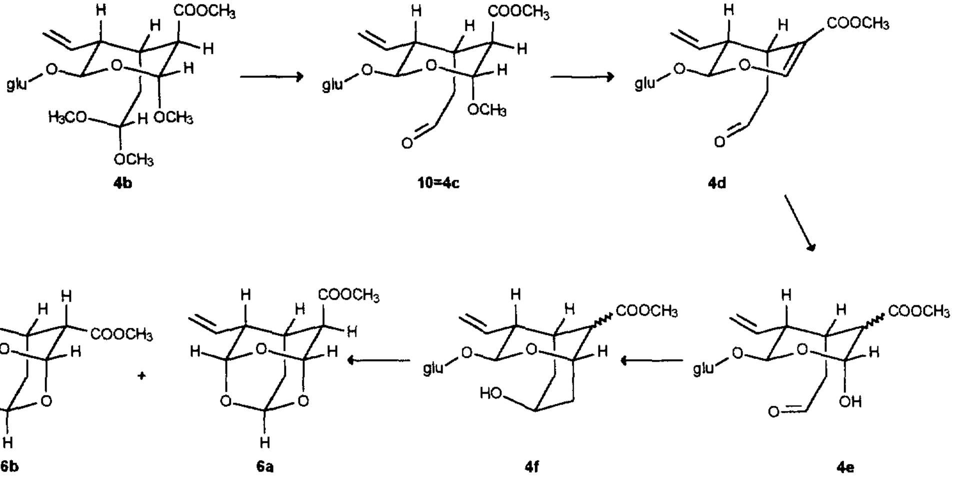
The single product of the acidic deglucosylation of **8** was the trioxadamantane derivative **9b** analogous to **7b** with bromine atom on C-4. This structure was supported by the close similarity of the ^{13}C- and ^{1}H NMR spectra of **9b** to the spectra of **7a** and **7b**. The signal of C-4 corresponds to a quaternary carbon suggesting that bromine is still present at C-4. The unambiguous assignment of the ^{1}H and ^{13}C NMR spectra of compound **9b** was based on a proton detected heteronuclear chemical shift correlation 2D measurement (HSQC)[11]. The *S* configuration of C-9 was proved by the measured nOe interaction between H-8 and H$_a$-6 (Table 1). The determination of the configuration of C-4 presented a special problem and was solved by heteronuclear nOe measurements. The two possible structures **9a** (the configuration of C-4 is *S*) and **9b** (the configuration of C-4 is *R*) are shown on Scheme 3. As it can be seen, the carbonyl carbon is close to H-9 in **9a** and to H$_b$-6 in **9b**. Selective irradiation of H-9 had no effect on the intensity of the signal of the carbonyl carbon, but irradiation of H$_b$-6 increased it. Thus C-4 has the configuration *R* corresponding to structure **9b** in Scheme 3. The configuration of C-4 of compound **8** probably did not change under the acidic deglucosylation, so it should have likewise *R* configuration.

Interpretation of the results: Educt **6** has three acetal units around C-1, C-3 and C-7, respectively. The acetal unit of C-7 is the most labile, as it could selectively be hydrolyzed to compound **10**. Both of the other acetal units at C-1 and C-3 have a center of chirality (C-4 and C-9, respectively) in α position. Under the reaction conditions applied by us, epimerisation at C-4 was demonstrated by isolation of the epimers **6a** and **6b**. At C-9, however, neither epimerisation, nor vinyl-ethylidene isomerisation was observed. This means that a free formyl group was not developped in major extent at this center of chirality. For rationalizing the reaction sequence in formation of the trioxadamantane structure, these experimental facts as well as the possibility of several equilibria should be considered.

In the conformational mixture of **4a** and **4b**, the reaction cascade starts with hydrolysis of the acetal unit around C-7. The formyl derivative **10=4c** may undergo elimination of methanol and addition of water affording compounds **4d** then **4e.** In these reactions epimerization at C-4 may occur. Reconstruction of the hemiacetal unit around C-7 gives **4f**. The final product as an epimeric mixture of **6a** and **6b** is formed by intramolecular transacetalisation and simultaneous removal of the glucosyloxy unit.

Formation of **7** and **9b** can be interpreted analogously. It should be noted that **9b** was formed as a single stereoisomer becaus as a consequence of the presence of the bromine atom, epimerisation could not take place at C-4 atom.

Scheme 4.



EXPERIMENTAL

NMR spectra were recorded at (^1H NMR 400 MHz; ^{13}C NMR 100 MHz) on a Bruker AC-400 instrument, or at (^1H NMR 200 MHz, ^{13}C NMR 50 MHz) on a Bruker AM-200 instrument using tetramethylsilane (TMS) as internal reference. The COSY and Hetcorr 2D spectra were measured with the standard microprograms of the DISNMR software. The 2D HSQC spectrum was measured using the pulse sequence described in reference[11], 1 ms purging pulse was applied to suppress the magnetization of ^1H directly bond to ^{12}C. The homonuclear DNOE measurements were performed using peak selective irradiation with the standard microprogram of the DISNMR software. The heteronuclear DNOE measurement was performed with peak selective irradiation. Attenuated 68 ms 90° proton pulses were applied 360 times consecutively on each peak of the multipletts, which resulted in a 28 sec irradiation time on each proton.

Secologanin dimethyl acetal (2)[8]: Compound **1** (390 mg, 0.001M) dissolved in anhydrous MeOH (3.9 ml) was stirred with acidic MSC-1 DOWEX ion exchange resin (390 mg) for 4h at room temperature. After filtration of resin, the solution was evaporated. Product **2** was yielded as a colorless foam (420 mg, 0.00096M, 96%). UV (MeOH) λmax 234 nm (logε=3.95); IR (KBr) 3800-3100, 1700, 1625 cm^{-1}. The ^1H NMR and ^{13}C NMR data of the product **2** are corresponding to the data of reference[8].

(3*R*,4*R*)-3,4-Dihydro-3-methoxysecologanin dimethyl acetal (4): Compound **2** (480 mg, 0.001M) and NaOH (90 mg, 0.0023M) was refluxed in a mixture of MeOH (3.0 ml) and H_2O (0.3 ml) for 8h, than stirred with acidic MSC-1 DOWEX ion exchange resin (720 mg) for 20 minutes at room temperature. After filtering out the resin and diluting with MeOH (4.5 ml), CH_2N_2 in Et_2O was added with stirring until the yellow color of CH_2N_2 was remained. After evaporation the product was chromatographed on silica gel (5 g) in CH_2Cl_2-MeOH-H_2O (320:50:6). Fractions 18-27 (each 1 ml) were combined and evaporated to afford pure **4**

amorphous oil (160 mg, 0.0003M, 30%). $[\alpha]_D$= -25.25° (MeOH, c=0.2%); IR (KBr) 3800-3100, 1720 cm^{-1}; ^{1}H NMR (($(CD_3)_2CO$, 400 MHz) δ 5.89(ddd, $J_{8,9}$=9.7, $J_{8,10}$=17.2, 10.4, H-8), 5.30-5.25(m, H_2-10), 5.21(d, $J_{3,4}$=8.9, H-3), 5.14(d, $J_{1,9}$=1.3, H-1), 4.70(d, $J_{1',2'}$=7.9, H-1′), 4.40(dd, $J_{6a,7}$=4.0, $J_{6b,7}$=7.7, H-7), 3.82(m, H_a-6′), 3.70-3.25(m, H-2′, H-3′, H-4′, H-5′, H_b-6′), 3.63(s, $COOCH_3$), 3.38(s, MeO-3), 3.23, 3.22(s, MeO-7), 2.60-2.50(m, H-5, H-9), 2.38(dd, $J_{4,5}$=12.1, H-4), 1.51(ddd, $J_{6a,6b}$=14.2 $J_{5,6a}$=10.4, H_a-6), 1.33(ddd, $J_{5,6b}$=3.6, H_b-6). ^{13}C NMR ($(CD_3)_2CO$, 50 MHz) δ 173.30(COO), 135.09(C-8), 120.14(C-10), 102.49(C-7), 99.02, 98.60, 98.55(C-1, C-3, C-1′), 78.32, 77.75(C-5′, (C-3′), 74.37(C-2′), 71.44(C-4′), 62.77(C-6′), 56.56(MeO-3), 53.83, 52.06(MeO-7), 51.77($COOCH_3$), 50.32(C-4), 45.08(C-9), 33.86(C-6), 31.83(C-5). Found: C, 51.7; H, 7.5. $C_{20}H_{34}O_{12}$ requires: C, 51.5; H, 7.4.

Compounds 6a and 6b: Compound **4** (500 mg, 0.001M) was dissolved in aqueous HCl (1 ml, 3.7%, 0.0001M) and to this was added toluene (6 ml). This reaction mixture was refluxed for 6h at 110°C with stirring. After separation, the aqueous phase was extracted two times with toluene (2x6 ml). The combined toluene phases were chromatographed after evaporation on silica gel (5 g) in Et_2O:C_6H_6:cyclohexane (1:2:2). Fractions 4-6 (each 3 ml) were combined and evaporated to afford pure **6a** and **6b** amorphous oil (110 mg, 0.0005M, 50%). IR (KBr) 1720, 1420 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 5.90-5.70(m, H-A3, H-B3, H-A8, H-B8), 4.93-5.10(m, H-A1, H-B1, H-A7, H-B7, H_2-B10, H_2-A10), 3.29(s, B-$COOCH_3$), 3.27(s, A-$COOCH_3$), 2.97(dm, $J_{8,9}$=7,0 H-A9), 2.57(t, $J_{3,4}$=$J_{4,5}$=2.4, H-A4), 2.48(m, H-A5, H-B4), 2.44(m, H-B5), 2.28(dm, $J_{8,9}$=7,0 H-B9), 2.00(m, H_a-A6, H_b-B6), 1.81(m, H_a-B6), 1.29(m, H_b-A6). ^{13}C NMR (C_6D_6, 100 MHz) δ A: 170.00(COO), 136.43(C-8), 117.55(C-10), 95.54(C-1), 92.98(C-3), 92.71(C-7), 51,41($COOCH_3$), 47.82(C-4), 41.74(C-9), 30.62(C-5), 29.88(C-6); B: 169.86(COO), 136.12(C-8), 117.48(C-10), 94.93(C-1), 93.43(C-7), 92.98(C-3), 51.41($COOCH_3$), 47.93(C-4), 46.11(C-9), 30.55(C-5), 26.04(C-6). A: **6a**, B: **6b.**

Hydrogenation of 2: 8,10-dihydrosecologanin dimethyl acetal (3): Compound **2** (434 mg, 0.001M) dissolved in MeOH was added to 108 mg of Pd-C (10%, Merck), previously suspended in MeOH (2 ml) and saturated with H_2. After 60 min reaction the suspension was filtered off and the methanolic solution was evaporated. The residue was a colorless foam, compound **3** (326 mg, 0.00075M, 75%). $[\alpha]_D$= -143.09° (MeOH, c=0.002%); IR (KBr) 1690, 1630 cm^{-1}; UV (EtOH) λmax 242 nm (log ε=4.06); ^{1}H NMR (CD_3OD, 200 MHz) δ 7.47(s, H-3), 5.42(d, $J_{1,9}$=8.2, H-1), 4.71(d, $J_{1'2'}$=8.2, H-1′), 4.42(t, $J_{7,6a}$=$J_{7,6b}$=5.5, H-7), 3.90(d, $J_{Ha6'Hb6'}$ =12.7, H_a-6′), 3.71(s, $COOCH_3$), 3.63(dd, $J_{5'.Hb6'}$=5.5, H_b-6′), 3.33, 3.23(s, MeO-7), 3.38-3.17(m, H-2′, H-3′, H-4′, H-5′), 2.87(dt, $J_{5,6a}$=9.7, $J_{5.9}$=$J_{5,6b}$=4.3, H-5), 1.81-1.29(m, H_2-8, H_2-6, H-9), 0.98(t, $J_{10,8}$=7.4, H_3-10). ^{13}C NMR (CD_3OD, 50 MHz) δ 169.55(COO), 153.86(C-3), 112.40(C-4), 105.08(C-7), 100.36(C-1′), 99.04(C-1), 78.34(C-3′), 77.96(C-5′), 74.76(C-2′), 71.60(C-4′), 62.80(C-6′), 54.09, 52.99, 51.83($COOCH_3$, MeO-7), 42.81(C-9), 34.34(C-6), 28.60(C-5), 20.66(C-8), 11.46(C-10). Found: C, 52.4; H, 7.4. $C_{19}H_{32}O_{11}$ requires: C, 52.3; H, 7.4.

(3*R*,4*R*)-3,4,8,10-Tetrahydro-3-methoxysecologanin dimethyl acetal (5): Compound **3** (440 mg, 0.001M) and NaOH (90 mg, 0.0023M) was refluxed in mixture of MeOH (3.0 ml) and H_2O (0.3 ml) for 8h, than stirred with acidic MSC-1 DOWEX ion exchange resin (720 mg) for 20 minutes at room temperature. After filtering out the resin and diluting with MeOH (4.5 ml) CH_2N_2 in Et_2O was added with stirring until the yellow color of

CH_2N_2 was remained. After evaporation the product was chromatographed on silica gel (6 g) in CH_2Cl_2-MeOH-H_2O (320:50:6). Fractions 7-14 (each 3.5 ml) were combined and evaporated to afford pure **5** colorless foam (345 mg, 0.00074M, 74%). $[\alpha]_D$= -19.92° (MeOH, c=0.2%); IR (KBr) 3426, 2925, 1794, 1132, 1075 cm^{-1}; ^1H NMR ($(CD_3)_2CO$, 400 MHz) δ 5.24(d, $J_{1,9}$=1.5, H-1), 5.14(d, $J_{3,4}$=8.7, H-3), 4.71(d, $J_{1'2'}$=7.9 H-1'), 4.32(dd, $J_{6a,7}$=4.8, $J_{6b,7}$=6.5, H-7), 3.83(m, H_a-6'), 3.70-3.25(m, H-2', H-3', H-4', H-5', H_b-6'), 3.63(s, $COOCH_3$), 3.36(s, MeO-3), 3.26, 3.23(s, MeO-7), 2.53(m, H-5), 2.29(dd, $J_{4,5}$=11.7, H-4), 1.65-1.25(m, H_a-6, H_b-6, H_a-8, H_b-8, H-9), 0.94(t, H_3-10). ^{13}C NMR ($(CD_3)_2CO$, 50 MHz) δ 173.61(COO), 103.09(C-7), 99.13(C-1′), 98.53(C-3), 96.75(C-1), 78.11, 77.47(C-5′ C-3′), 74.27(C-2′), 71.24(C-4′), 62.66(C-6′), 56.50(MeO-3), 53.61, 52.28(MeO-7), 51.76($COOCH_3$), 50.20(C-4), 41.35(C-9), 33.25(C-6), 32.42(C-5), 18.17(C-8), 12.82(C-10). Found: C, 51.3; H, 7.5. $C_{20}H_{36}O_{12}$ requires: C, 51.2; H, 7.7.

Compounds 7a and 7b: Compound **5** (400 mg, 0.00085M) was dissolved in aqueous HCl (1 ml, 3.7%, 0.0001M) and to this toluene (6 ml) was added. The reaction mixture was refluxed for 6h at 110°C with stirring. After separation, the toluene phase was chromatographed on silica gel (4 g) in Et_2O-C_6H_6-cyclohexane (1:2:2). Fractions 2-4 (each 6 ml) were combined and evaporated to afford the mixture of **7a** and **7b** as amorphous oil (135 mg, 0.0006M, 70%). IR (KBr) 2960, 1738, 1187, 1087 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.77(t, $J_{3,4}$=2.2, H-A3), 4.99-4.95(m, H-A1, H-A7 H-B1, H-B7), 3.31(s, B-$COOCH_3$), 3.29(s, A-$COOCH_3$), 2.61(t, $J_{4,5}$=2.2, H-A4), 2.53(m, H-B4), 2.40(m, H-A5 H-B5), 2.03(m, H-A9), 1.84(dt, $J_{6a,6b}$=13.2, $J_{5,6a}$=2.8, $J_{6a,7}$=2.8, H_a-A6), 1.82 (m, H_a-B6) 1.67(m, H_b-B6), 1.40-1.15(m, H_b-A6, H_2-A8, H_2-B8), 0.69(t, H_3-A10, H_3-B10). ^{13}C NMR (C_6D_6, 50 MHz) δ A: 170.16(COO), 95.83(C-1), 93.36(C-3), 92.69(C-7), 51.34($COOCH_3$), 48.39(C-4), 39.37(C-9), 29.62(C-6), 29.07(C-5), 22.36(C-8), 11.04(C-10) B: the signals of this isomer were not observed because of its low concentration. A: **7a**, B: **7b**.

(3*R*,4*R*)-4-Bromo-3,4,8,10-tetrahydro-3-methoxysecologanin dimethyl acetal (8): To compound **3** (440 mg, 0.001M), dissolved in anhydrous MeOH (12.5 ml) solid $BaCO_3$ (3.6 g) was added and than a solution of Br_2 (0.06 ml) in anhydrous MeOH (27 ml) was added dropwise. The reaction mixture was stirred for 2.5h at 0° C in dark, than the unreacted Br_2 was removed with tetraline (5 drops). The residue of filtered, than evaporated solution was suspended in H_2O (25 ml). This aqueus suspension was extracted twice with Et_2O (2x10 ml), to remove tetraline, than evaporation resulted in an oil, which was chromatographed on silica gel (15 g) in CH_2Cl_2-MeOH-H_2O (320:50:6). Fractions 26-42 (26-35 each 5 ml, 37-42 each 10 ml) were combined and evaporated to afford pure **8** as colorless amorphous foam (350 mg, 0.00064M, 64%). $[\alpha]_D$= -29.99° (MeOH, c=0.2%); IR (KBr) 3600-3100, 1730 cm^{-1}; ^1H NMR (C_6D_5N, 60 °C 400 MHz) δ 5.72(s, H-3), 5.66(d, $J_{1,9}$=6.1, H-1), 5.33(d, $J_{1',2'}$=7.8, H-1′), 4.67(dd, $J_{6a,7}$=5.0 $J_{6b,7}$=6.3, H-7), 4.42(dd, $J_{6'a,6'b}$=11.7, $J_{5',6a}$=3.0 H_a-6′), 4.28(dd, $J_{5',6'a}$=5.4 H_b-6′), 4.18(m, H-2′, H-4′), 4.02(m, H-3′), 3.91(m, H-5′), 3.76(s, $COOCH_3$), 3.64(s, MeO-3), 3.35, 3.32(s, MeO-7), 3.08(dt, $J_{5,6a}$=4.0, $J_{5,6b}$=6.7, $J_{5,9}$=4.0, H-5), 2.51(dt, $J_{6a,6b}$=15.3, H_a-6), 2.46(m, H-9), 2.15(dt, H_b-6), 1.87(dkv, $J_{8a,8b}$=14.6, $J_{8a,9}$=7.3, $J_{8,10}$=7.3, H_a-8), 1.61(dkv, $J_{8b,9}$=7.3, H_b-8), 0.94(t, H_3-10). ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ 169.00(COO), 105.59, 102.82 (C-1), (C-3), 99.66(C-1′), 95.21(C-7), 78.15, 77.84(C-3′) (C-5′), 74.58(C-2′), 71.61(C-4′), 66.57(C-4), 62.85(C-6′), 57.24(MeO-3), 54.74($COOCH_3$), 53.00, 52.92(MeO-7), 43.77(C-9), 41.45(C-5), 32.71(C-6), 19.10(C-8), 10.03(C-10). Found: C, 43.7; H, 6.4; Br, 14.4. $C_{20}H_{35}BrO_{12}$ requires: C, 43.9; H, 6.5; Br, 14.6.

Compound 9b: Compound **8** (550 mg, 0.001 M) was dissolved in aqueous HCl (1 ml, 3.7%, 0.0001M) and to this toluene (6 ml) was added. The reaction mixture was refluxed for 6h at 110°C with stirring. After separation, the toluene phase was chromatographed on silica gel (30 g) in Et_2O-C_6H_6-cyclohexane (1:3:6). Fractions 12-18 (each 6 ml) were combined and evaporated to afford pure **9b** as brown amorphous foam (164 mg, 0.00045M, 45%). $[\alpha]_D$= 23.89° (MeOH, c=0.2%); IR (KBr) 1740cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.50(d, $J_{3,5}$=2.2, H-3), 5.08(q, $J_{6a,7}$=2.0, $J_{6b,7}$=2.0, $J_{1,7}$=2.0, H-7), 5.04(t, $J_{1,9}$=2.0, H-1), 3.88(s, $COOCH_3$), 2.80(m, H-5), 2.62(tt, $J_{8a,9}$=7.5, $J_{8b,9}$=7.5, $J_{5,9}$=2.0, H-9), 2.32(ddd, $J_{6a,6b}$=14.1, $J_{5,6a}$=3.4, H_a-6), 2.13(dq, $J_{5,6b}$=2.3, H_b-6), 1.76(dkv, $J_{8a,8b}$=14.5, , $J_{8,10}$=7.5, H_a-8), 1.55(dkv, H_b-8), 1.02(t, H_3-10). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.68(COO), 94.57(C-1), 94.15(C-3), 92.01(C-7), 61.23(C-4), 53.33($COOCH_3$), 38.91(C-9), 35.83(C-5), 28.99(C-6), 21.83(C-8), 11.17(C-10).

(3*R*,4*R*)-3,4-Dihydro-3-methoxysecologanin (10): Compound **4** (100 mg, 0.00023M) dissolved in water (10 ml) was stirred with acidic MSC-1 DOWEX ion exchange resin (100 mg) for 3.5h at 70°C. After filtering out the resin and evaporating the product was chromatographed on silica gel (6.5 g) in CH_2Cl_2-MeOH-H_2O (320:50:5). Fractions 8-11 (each 8 ml) were combined and evaporated to afford pure **10** as amorphous oil (27 mg, 0.00007M, 30%). IR (KBr) 3433, 1734 cm^{-1}; ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ 9.64(t, $J_{7,6a}$=$J_{7,6b}$=1.4, H-7), 5.88(dt, $J_{8,10a}$=17.0, $J_{8,10b}$=$J_{8,9}$=10.2, H-8), 5.27(d, $J_{3,4}$=8.9, H-3), 5.26(dd, $J_{10a,10b}$=2.2, H_a-10), 5.18(d, $J_{1,9}$=1.3, H-1), 5.17(dd, H_b-10), 4.74(d, $J_{1',2'}$=7.6, H-1'), 3.61(s, COOCH3), 3.41(s, MeO-3), 3.06(m, H-5), 2.53(m, H_a-6, H-9), 2.39(dd, $J_{4,5}$=12.3, H-4), 2.25(ddd, $J_{6a,6b}$=17.7, $J_{6,5}$=5.3, H_b-6). ^{13}C NMR ($(CD_3)_2CO$, 50 MHz) δ 201.04(C-7), 172.74(COO), 134.60(C-8), 120.45(C-10), 98.88, 98.45, 97.94(C-1, C-3, C-1′), 78.30, 77.88(C-5′, C-3′), 74.48(C-2′), 71.51(C-4′), 62.82(C-6′), 56.73(MeO-3), 51.94($COOCH_3$), 49.75(C-4), 45.86(C-9), 45.56(C-6), 30.80(C-5).

(3*R*,4*R*)-3,4,8,10-Tetrahydro-3-methoxysecologanin (11): Compound **5** (100 mg, 0.00023M) dissolved in water (10 ml) was stirred with acidic MSC-1 DOWEX ion exchange resin (100 mg) for 3.5h at 70°C. After filtering out the resin and evaporating the product was chromatographed on silica gel (6.5 g) in CH_2Cl_2-MeOH-H_2O (320:50:5). Fractions 9-12 (each 8 ml) were combined and evaporated to afford pure **11** as amorphous oil (26 mg, 0.00007M, 30%). IR (KBr) 3454, 1731 cm^{-1}; ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ 9.64(t, $J_{7,6a}$=$J_{7,6b}$=1.8, H-7), 5.29(d, $J_{1,9}$=1.6, H-1), 5.21(d, $J_{3,4}$=8.7, H-3), 4.76(d, $J_{1'2'}$=7.7, H-1'), 3.60(s, COOCH3), 3.39(s, MeO-3), 3.08(m, H-5), 2.56(ddd, $J_{6a,6b}$=17.1, $J_{6a,5}$=7.3, H_a-6), 2.37(ddd, $J_{6b,5}$=4.9, H_b-6), 2.34(dd, $J_{4,5}$=11.6, H-4), 1.66-1.21(m, H_2-8, H-9), 0.93(t, $J_{10,8}$=7.3, H_3-10). ^{13}C NMR ($(CD_3)_2CO$, 50 MHz) δ 201.35(C-7), 172.98(COO), 99.19(C-1′), 98.49(C-3), 96.59(C-1), 78.27, 77.77(C-3′, C-5′), 74.51(C-2′), 71.57(C-4′), 62.88(C-6′), 56.65(MeO-3), 51.90(COOCH3), 49.78(C-4), 45.32(C-6), 42.56(C-9), 31.02(C-5), 18.59(C-8), 12.92(C-10).

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